REMARKS

Claims 41, 42 and 78-85 were pending in the subject application. By this amendment, Claims 78, 80, 83 and 85 have been canceled without prejudice or disclaimer, and Claims 41, 42, 79, 81, 82 and 84 have been amended. Applicant maintains that the amendments do not raise an issue of new matter. Support for the amendments to Claim 41 can be found at least in Claim 42, and in the application as filed at least on page 5, line 4, and the paragraph spanning pages 15-16. Support for the amendments to Claim 81 can be found at least in Claim 82, and in the application as filed at least on page 5, line 4, the paragraph spanning pages 15-16, Example 2 on page 17, and Table 2 on page 20. Support for the remaining claim amendments can be at least in the previous version of the claims. Accordingly, entry of the amendment is respectfully requested.

Rejection under 35 U.S.C. §102(b)

Claim 41 and dependent Claims 78 and 79 are rejected as being anticipated by Wirz-Justice et al. (Alzheimer Disease and Associated Disorders 14(4): 212-215, 2000).

Claim 41 has hereinabove been amended to recite the limitation based on Claim 42, i.e. "pipamperone in a dose of 5-15 mg..." thereby obviating this rejection.

Rejections under 35 U.S.C. §112

1. Claims 41, 42, 78, 79, and 81-84 are rejected as not enabled for the full scope of diseases disorders recited in the claims.

Independent Claims 41 and 81 have hereinabove been amended to specify the disorder recited in Claims 80 and 85 (mood disorder) and anxiety disorder. Thus, the claims specify (a) pipamperone in a dose of 5-15 mg, and (b) a selective serotonin re-uptake inhibitor.

The inventor provides an explanation for the advantage of this combined treatment, as set forth on pages 8-9 of the current application:

> "The inventors found that the non-response to selective serotonin re-uptake inhibitors (SSRIs) in depression may be declared by (partial) inhibition of the 5-HT1A stimulation via 5-HT2A stimulation. Des-inhibition thereof via 5-HT2A antagonism seems to be an answer to this problem.
>
> The present inventors found that a simultaneous or foregoing treatment with a compound having a high selective 5-HT2A antagonist, inverse agonist or partial agonist activity, could lead to a greater response towards SSRIs. However, not all compounds exhibiting 5-HT2A antagonism are useful: competition between 5-HT2A stimulation via serotonin and 5-HT2A antagonism via the compound could be responsible for the lack of more efficacy of compounds which have both a selective serotonin re-uptake inhibitory and 5-HT2A antagonist profile, such as trazodone and nefazodone.
>
> The present inventors further surprisingly found that a simultaneous or foregoing treatment with a compound having a high selective D4 antagonist, inverse agonist or partial agonist activity in combination with a compound having a high selective 5-HT2A antagonist, inverse agonist or partial agonist activity could lead to a greater response towards SSRIs.
>
> The present inventors found that a compound which binds to the 5-HT2A receptor with a pKi of at least 8 but for which the binding affinity, ie pKi, towards other 5HT receptors is less than 8 in combination with a compound which has a high selective affinity for the D4 receptor, i.e. which bind to the D4 receptor with a pKi of at least 8 but for which the binding affinity, ie pKi, towards other dopamine receptors is less than 8 also show such an improved effect in treatment. These effects, ie D4 antagonism, inverse agonism or partial agonism and 5-HT2A antagonism, inverse agonism or partial agonism, preferably reside in the same compound."

Applicant would also like to direct the Examiner's attention to applicant's Experimental Examples presented in related U.S. Patent Application Nos. 10/984,683 [US 2005/0203130] and 10/580,962 [US 2007/0078162]. The Examples show the advantages of using pipamperone with citalopram to treat depression (Example 3), obsessive-compulsive disorder (Example 4), and panic disorder (Example 5). Obsessive-compulsive disorder and panic disorder are types of anxiety disorders (see, for example, "Diagnostic and Statistical Manual of Mental Disorders" published by the American Psychiatric Association, which is referred to in the first full paragraph on page 11 of the present application).

Reconsideration and withdrawal of this rejection are respectfully requested.

2. Claims 81-85 are rejected under the written description requirement. The Examiner indicated that the application does not provide support for a pharmaceutical composition consisting of only the two specified compounds. Claim 81 has hereinabove been amended to clarify that the two specified compounds are the two pharmaceutically active ingredients in the composition. The application, for example, in Example 2 on page 17 and Table 2 on page 20 describes the set-up of a clinical trial, in which patient groups are administered a combination of only pipamperone and citalopram.

Reconsideration and withdrawal of this rejection are respectfully requested.

Rejections under 35 U.S.C. §103(a)

1. Claims 41, 42 and 80 are rejected as being unpatentable over Dudley et al. (US 2004/0002482), in view of Wirz-Justice et al. (Alzheimer Disease and Associated Disorders 14(4): 212-215, 2000) and Medicaments Psychotropics.

Applicant respectively traverses this rejection.

The present invention

Before considering the cited art, applicant would like to provide the Examiner with an overview of the present invention. In particular, the claimed invention requires the administration of pipamperone in an unprecedented low dose of 5 to 15 mg.

One of the main problems with contemporaneous psychoactive drugs is their side effects, which limit the usability of these drugs. For instance, the selective serotonin re-uptake inhibitors (SSRIs), which are generally considered to be the first-line antidepressants of choice, block the serotonin transporter responsible for pre-synaptic reuptake. Thus, the availability of synaptic serotonin is augmented, leading to a *stimulation* of various serotonin (5-HT) receptors. However, the simultaneous stimulation of the pre- and postsynaptic serotonin receptors results in several inhibitory effects. Hence, administration of SSRIs causes a negative feedback, which limits the antidepressant actions of these drugs.

The present inventor surprisingly found that the use of a *daily low dose of 5 - 15 mg* of pipamperone augments the effect of a SSRI in treating a disease or disorder with an underlying dysregulation of the emotional functionality.

Dose-effect of pipamperone: The inventor surprisingly found that at the claimed daily low dose, pipamperone has a specific, but double effect, *i.e.* a high selective D4 *and* 5-HT2A receptor antagonistic effect. As such, pipamperone can exert its augmenting effect on the second, SSRI compound. This effect has not been described in the prior art, nor is there any hint towards such an effect. This daily low dose of pipamperone has *not* been used in the prior art.

Pipamperone as a sedative neurolepticum: In the prior art, pipamperone is used at higher doses acting as a *sedative neurolepticum* (see e.g. Squelart as well as the manufacturer's instructions, both of record). As a corollary, the prior art teaches to use the highest tolerable dose for treating psychoses. However, at these higher doses

pipamperone has no therapeutic effect on the SSRI because an antagonistic activity towards the *D2* and *alpha-adrenergic* receptor takes place, which dominates the clinical effect. This is well-known in the art. This antagonistic activity happens in such a way that negative emerging symptoms like D2 antagonistic related signs as emotional blunting and cognitive problems (the so-called "neuroleptic induced deficit syndrome") and alpha-adrenergic related signs such as dizziness, decreased blood pressure and drowsiness may counteract the symptoms of, but certainly not treat, and least of all, augment the effect of the SSRI in the treated mood or anxiety disorder.

Synergy of low doses pipamperone and selective serotonin receptor inhibitors: Administration of SSRIs has a two-fold effect: the plasma membrane serotonin reuptake transporter is blocked, *i.e.* the effect sought after, and the availability of synaptic serotonin is augmented. The latter effect results in a *stimulation* of the 5-HT receptors, which causes several inhibitory effects that limit the actions of these drugs.

The present inventor demonstrated that pipamperone at low doses realizes a highly selective D4 and 5-HT2A receptor antagonistic effect, because of which serotonin resulting from the SSRI cannot bind to the serotonin 2A receptor. As a corollary, the efficacy of the SSRI is increased, but also the cognitive and behavioural problems induced by enhanced D4 stimulation in the meso-cortical cortex as a result of the augmented availability of dopamine via 5-HT2A antagonism is prevented.

The present invention does not involve a mere optimization of dosage by routine experimentation as suggested by the Examiner. Rather, it is well-known that pipamperone at the ubiquitously used (high) prior art doses indeed decreases the symptom of psychological anxiety (see e.g. "Dipiperon" of record). This effect of pipamperone results from a neuroleptic-sedative effect. Specifically, it is known that the high dose pipamperone results in D2 receptor-related dopaminergic and H1 receptor-related histaminergic antagonism, which is responsible for the neuroleptic-sedative effect. This

antagonizing effect (resulting in this neuroleptic-sedative effect) is absent at the claimed low dose of 5-15 mg/day. Accordingly, there would be no incentive to decrease the amount of pipamperone administered, since this would lower the neuroleptic-sedative effect.

Indeed, as previously detailed, the prior art teaches away from using a low dose.

For instance, Dipiperon (of record) teaches away from this low dose range. For adults, Dipiperon on page 1 teaches an initial dose of 40 to 80 mg a day, and that if necessary the dose may be increased to a maximum of 360 mg per day. For children the initial dose is 20 mg per day, and the optimal therapeutic dose varies from 20 to 40 mg per day. There is no teaching or suggestion in the cited references to administer pipamperone at a lower dose than the recommended dose. To the contrary, the teaching is always to increase the dose.

Dudley

In essence the Examiner asserts that Dudley discloses the following: combinations for treating or preventing depressive disorders, where the compositions can include pipamperone or citalopram. The Examiner acknowledged that Dudley does not teach both pipamperone and citalopram in the same composition. The Examiner indicated that the person skilled in the art would be motivated to make such a combination in view of both compounds being described as useful for treating depression; and achieve a synergistic and/or additive effect of the combination.

Dudley relates to subject failing to respond to conventional antidepressants: Applicant notes that Dudley aims at and relates to treating a depressive disorder by administering percutaneously compositions and combinations comprising a steroid in the testosterone synthetic pathway in subjects *failing to respond to conventional antidepressants* and/or who exhibited low or borderline testosterone levels (see paragraph 29). This is illustrated in

Example 12, using a testosterone transdermal gel, where it is noted that the subjects were "taking adequate dose of antidepressant medication ... but still complaining of depressive symptoms..." (paragraph 0508).

Dudley teaches an alternative: Dudley provides an alternative for subjects failing to respond to conventional antidepressants, in particular the use of testosterone. The use of testosterone pervades throughout the detailed description. The use of testosterone as the primary compound is explicitly confirmed in paragraphs 119 - 121, 148 - 162, the Examples in general, Examples 1 - 9 (paragraphs 246 - 492) in particular, paragraphs 472-473 relating to mood assessment in response to testosterone alone, the Figures and, first and foremost, the claims. Dudley provides testosterone as an alternative therapy for treating depressive disorders.

Exceptionally, Dudley provides that a further compound may be administered in conjunction with testosterone. Hence, the first compound is always and invariantly testosterone or a steroid in the testosterone synthetic pathway even in a combination of compounds. Paragraph 122 relates to "methods, kits, combinations and compositions" which are used *in conjunction* with a pharmaceutical agent, such as an antidepressant. In paragraph 124 "the present invention employs testosterone *in conjunction* with a pharmacologically-effective amount of ... an anti-depressant" (emphasis added). The term "methods, kits, combinations and compositions for treating ...." used in Dudley, always comprises testosterone and possibly a second compound. In paragraphs 131 - 133, the antidepressant agents which can be used *in conjunction* with testosterone are exemplified. Although it is mentioned in the last sentence that combinations can be used of the antidepressants, these combinations are to be used *in conjunction* with testosterone. Hence, when considering Dudley the person skilled in the art would be taught administering at least testosterone when treating depression. In Claims 81, 82 and 84 of the instant invention, the pharmaceutical composition contains the recited components as

the active pharmaceutical ingredients and cannot include testosterone as a pharmaceutically active ingredient.

Dudley does not teach any combination having a beneficiary effect: Dudley does not disclose any example relating to any combination medication (comprising two non-testosterone compounds) having any effect, even less to a beneficiary effect, even less to a combination comprising two conventional anti-depressants, even less to a combination comprising pipamperone, and least of all a combination comprising pipamperone and citalopram.

It is noted that most examples in Dudley are prophetic, *i.e.* Examples 1-4, 6-9, Example 2 on page 55, and Example 11. Example 5 relates to methods of improving sexual performance and increasing libido in hypogonadal men. Example 10 relates to treatment of hypogonadism in male subjects. Example 12 relates to a method of treating a depressive disorder in a subject. In paragraph 0508 it is noted that "Men age 30-65 years, presently taking an adequate dose of antidepressant medication (as defined by the manufacturer's published product information) for at least the last four weeks, but *still complaining of depressive symptoms* sufficient to meet the DSM IV criteria for current major depressive disorder" (emphasis added). Testosterone was added to the antidepressant medication. Neither Pipamperone nor citalopram was used.

Isolating the combination citalopram - pipamperone amounts to undue burden: There is no incentive in Dudley to combine citalopram with pipamperone. Furthermore, neither of these compounds is a preferred compound (paragraph 133). In paragraph 132, over 140 antidepressants are listed. Each and every combination would encompass about 10^{158} possibilities. Even if only a combination of only two compounds is contemplated (which is denied), about 10,000 possibilities are disclosed. It would amount to undue burden to test each and every combination in order to come to pipamperone and citalopram (in particular considering that the subjects failed to respond to conventional

antidepressants). In addition, further to the teachings of Dudley, any combination should be tested with at least three compounds, *i.e.* including testosterone.

Wirz-Justice

The Examiner asserts that Wirz-Justice teaches a combination of pipamperone (20-30 mg) and citalopram (10 mg) (Table 1, page 214).

Rather, applicant respectfully notes that Wirz-Justice teaches administering citalopram (10 mg/d) to a subject already receiving the combination of risperidone (2-3 mg/d) and pipamperone (20-30 mg/d) (Table 1, page 214 left column). Wirz-Justice evaluated different drug combinations on the rest-activity cycle in Alzheimer disease. Wirz-Justice teaches that the effect of citalopram as an addition to the risperidone/pipamperone combination leads to a rest-activity cycle alteration, more specifically a peak of morning activity, less afternoon activity, and less movement during the first part of the night, in combination with a shift of the cycle to earlier. In conclusion, Wirz-Justice teaches the use of citalopram with a combination of risperidone and pipamperone, pipamperone at a high dose (20-30 mg/d), and the use of this combination to harmonize the rest-activity cycle in Alzheimer Disease. Wirz-Justice is silent about mood or anxiety disorders.

Medicaments Psychotropes

The Examiner asserts that Medicaments Psychotropes teaches an initial daily dose of 10 mg of pipamperone to be administered.

Applicant respectfully notes that Medicaments Psychotropes teaches the dose of Dipiperon for children over the age of 5. A daily dose of 50 mg is recommended for the youngest child, i.e., a child of age 5 (5 drops per year of age ("5 gouttes x année d' âge") where 5 drops = 10 mg. This dose is accomplished by starting off with 10 mg (5 drops)

on day one and increasing the dose with 10 mg (5 drops) per day until the final needed treatment dose is reached. Thus, it is recommended in Medicaments Psychotropes that children only start with a dose of 10 mg per day. This dose is subsequently increased by 10 mg per day to the daily dose that is recommended for the age of the child (e.g. 50 mg per day for a child of age 5 years, with higher doses for older children). In other words, the treatment dose is not the start dose.

Medicaments Psychotropes does *not* provide any information whatsoever on disorders or diseases that can be treated, even less on treating mood or anxiety disorders.

In conclusion, applicant respectfully maintains that a person of ordinary skill in the art would never combine the teachings of documents Dudley, Wirz-Justice and Medicaments Psychotropes to arrive at the subject-matter of the claims of the current application for at least the following reasons:

- it requires impermissible hindsight to single out pipamperone, which is neither preferred nor detailed further, out of the more than 140 compounds listed in Dudley;
- it requires impermissible hindsight to combine pipamperone with an SSRI in view of Dudley;
- it requires undue burden to test each and every envisaged combination (10^{158}) of Dudley to come to the presently claimed combination;
- it requires impermissible hindsight to lower the dose of pipamperone in view of Dudley, since Dudley uses pipamperone as an antidepressant (i.e. by necessity at a high dose; see above);
- it requires impermissible hindsight to combine Dudley with Wirz-Justice, since Dudley relates to mood disorders only, while Wirz-Justice relates to Alzheimer Disease only.

- it requires impermissible hindsight to combine Dudley or Wirz-Justice with Medicaments Psychotropes, which is completely silent on any indication; and
- the cited references do not provide any teaching or motivation to use the claimed treatment dose of 5-15 mg pipamperone.

Reconsideration and withdrawal of this ground of rejection are respectfully requested.

2. Claims 81-85 are rejected as being unpatentable over Bymaster et al. (WO 98/11897), in view of Wirz-Justice et al. (Alzheimer Disease and Associated Disorders 14(4): 212-215, 2000), Mack et al. (Neuropsychopharmacology 28: 402-412, 1991) and Medicaments Psychotropics.

Applicant respectively traverses this rejection.

Wirz-Justice and Medicaments Psychotropes have been discussed above.

Bymaster

The Examiner indicates that Bymaster teaches a composition comprising an antipsychotic and a serotonin reuptake inhibitor.

Applicant respectfully notes that the claims as herein amended require the combination of pipamperone and a selective serotonin re-uptake inhibitor. Bymaster does not teach the use of pipamperone.

Marek

The Examiner indicates that Marek teaches that the combination of 5-HT_{2A} blocking agents and SSRIs exhibits synergistic action in neuropsychiatric disorders.

Applicant notes that Marek hypothesizes that "5-HT_{2A} receptors actually oppose the therapeutic effects of activating non-5-HT_{2A} receptors in diverse neuropsychiatric

syndromes such as depression, OCD, and PPDs" (p.407, Col.1, penultimate paragraph). However, Marek is uncertain of the cause: "The target receptor(s) that actually mediate the therapeutic effects of increased synaptic 5-HT caused by SSRIs is far from clear and may be different for these and other psychiatric syndromes."

Marek concludes that "[t]he most parsimonious explanation for these findings is that blockade of the 5-HT_{2A} receptors and activation of non-5-HT_{2A} receptors may have similar effects" (p.408, col.2, emphasis added); and "[s]upport for the hypothesis that blockade of the 5-HT_{2A} receptors coincident with activation of the non-5-HT_{2A} receptors results in more robust clinical activity than either drug alone could come from clinical testing of highly selective 5-HT_{2A} antagonists..." (p.408, col.2, emphasis added). Thus, Marek teaches to activate non-5-HT_{2A} receptors, and ignores the importance of D4 antagonism. Not only is Marek wholly silent on D4 antagonism, Marek does not disclose that pipamperone is a selective D4 antagonist (cf. p.407, col.1, 1st full paragraph).

In contrast, the present inventor realized that there is a complex balance of regulation of inhibitory and excitatory signaling by 5-HT_{2A} activation, which necessitates specifically antagonizing both the 5-HT_{2A} and the D4 receptors by pipamperone (in order to augment the effect of an SSRI). This specific effect is only achieved at low doses pipamperone (cf. Table 1 of the application).

In contrast to Marek, the present inventor also realized that 5-HT_{2A} antagonism must be accompanied by D4 receptor antagonism, since 5-HT_{2A} antagonism results in the augmented availability of dopamine. Increased availability of dopamine in turn leads to cognitive and behavioral problems induced by enhanced D4 receptor stimulation in the meso-cortical cortex. D4 receptor antagonism prevents the cognitive and behavioral problems induced by 5-HT_{2A} antagonism.

Marek prefers the use of risperidone, which is the most potent and selective 5-HT_{2A} receptor antagonist (see p.403, col.2). Marek does not prefer pipamperone, does not

teach pipamperone in combination with an SSRI, does not suggest lowering the dose of any compound of the combination, does not suggest lowering the dose of the 5-HT_{2A} receptor antagonist, does not imply, let alone recognize the importance of D4 receptor antagonism, and teaches away from the present invention by stressing the activation (not antagonism) of the non-5-HT_{2A} receptors (e.g. D4-receptor).

No motivation to combine pipamperone with an antidepressant: Applicant respectfully maintains that in view of the manufacturer's instructions ("Dipiperon"), both Dudley and Marek mischaracterize pipamperone as an antidepressant. "Dipiperon" clearly indicates "Depression of the central nervous system" as a contraindication for its usage. Under "Special warnings and precautions for use," "Dipiperon" indicates "Major Depression can become visible as a result of antipsychotics." Under "Interactions with other medicinal products and other forms of interaction," "Dipiperon" indicates "The simultaneous use of other antipsychotics, lithium, antidepressants, anti-Parkinson medicines and drugs with a central anticholinergic effect increases the risk of the occurrence of tardive dyskinesia." Under "Undesirable effects," "Dipiperon" indicates "The following side effects may also occur: ... worsening of depressions..." Thus, the instructions of the manufacturer teach against the combination of pipamperone and antidepressants. A person of ordinary skill in the art would not be motivated to use pipamperone as an antidepressant. Further, Applicant notes that Ansoms et al. (1977), to which Marek refers for characterizing pipamperone as an antidepressant, teaches the use of pipamperone to relieve sleep disorders in depressed patients, which is different than using pipamperone to treat depression.

Applicant respectfully maintains that a person of ordinary skill in the art would not combine the teachings of documents Bymaster, Wirz-Justice, Mack and Medicaments Psychotropics to arrive at the subject-matter of Claim 81 and its dependent claims.

Reconsideration and withdrawal of this ground of rejection are respectfully requested.

Status of Related European Application

Applicant would like to direct the Examiner's attention to related European Patent Application No. 04025035.9. Enclosed is a copy of a February 19, 2009 Decision to grant a European patent based on the application and of a October 13, 2008 Communication indicating that the Examining Division of the European Patent Office intends to grant a European patent on the basis of the application as attached to the Communication. The application was allowed with broad claims including uses of pipamperone and a SSRI for treating a mood disorder or anxiety disorder.

Status of U.S. Patent Family Members

Applicant would also like to advise the Examiner of the status of co-pending patent family members.

1. U.S. Patent Application No. 10/752,423. The claims have been subject to a restriction requirement. Office Actions on the merits of the application issued on October 2, 2007, May 13, 2008 and February 19, 2009.

2. U.S. Patent Application No. 10/803,793. The claims have been subject to a restriction requirement. Office Actions on the merits of the application issued on May 3, 2007, October 19, 2007, September 2, 2008 and February 20, 2009.

3. U.S. Patent Application No. 10/984,683. The claims have been subject to a restriction requirement. Office Actions on the merits of the application issued on August 10, 2007, February 22, 2008, and October 21, 2008.

4. U.S. Patent Application No. 10/580,962. The claims have been subject to a restriction requirement issued on March 6, 2009.

Supplemental Information Disclosure Statement

In accordance with the duty of disclosure under 37 C.F.R. §1.56, applicant would like to direct the Examiner's attention to the references that are listed on the attached form PTO/SB/08A-B (2 pages).

CONCLUSIONS

In view of the amendments and remarks made hereinabove, reconsideration and withdrawal of the rejections set forth in the September 15, 2008 Office Action and passage of the pending claims to allowance are respectfully requested. If there is any minor matter preventing the allowance of the subject application, the Examiner is requested to telephone the undersigned attorney.

A check for $735.00 is enclosed for a small entity for the $555.00 fee for a three month extension of time and the $180.00 fee for filing an Information Disclosure Statement. No additional fee is deemed necessary in connection with the filing of this response. However, if any other fee is required to preserve the pendency of the subject application, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 01-1785. Overpayments may also be credited to Deposit Account No. 01-1785.

Respectfully submitted,

AMSTER, ROTHSTEIN & EBENSTEIN LLP
Attorneys for Applicant
90 Park Avenue
New York, New York 10016
(212) 336-8000

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New York, New York

By _____
Alan D. Miller, Reg. No. 42,889